WBMT Graft Processing Workshop

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Graft Processing

- Integral part of the transplant programme
- Specialised manpower and equipment: ?cost factored into transplant calculation
- Minimal to advanced extensive processing
- Stem cell sources: BM vs PBSC vs Cord
- Essential parameter in determining engraftment; graft versus host disease; immune reconstitution; relapse

Main functions:

-Overseeing the safe receipt/handling of donor stem cells
-Defining the product: its quality and characteristics----Francesco Lanza
-any manipulation required for the transplant---- Francesco Lanza

-Safe delivery back to the hospital/patient including infectious diseases

-quality assurance

Minimal Requirements and Essential Features for Setting up a Stem Cell Processing Laboratory.

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- On behalf of the Graft Processing Subcommittee of the Worldwide Network for Blood and Bone Marrow Transplantation (WBMT).

Scope of Talk

- Physical Layout and considerations
- Equipment/reagents and personnel needed
- Range of Processing Services offered
- Guidance documents and resources

Key Considerations

- Access to reliable electricity supply
- Minimally Manipulated Products in support of a transplant programme: not Haplo-identical or advanced cell processing
- improvements will be made as additional resources become available and as volume and scope of clinical transplant services increase

Physical Considerations

- **Does every transplant programme require a processing lab?**
- **Does centralising reduce costs and make best use of manpower?**
- **Number of centres; transplant numbers; distances from lab to centres**
- Hospital based vs involvement of the Transfusion Service
- Examples of processing labs in the UK and Singapore

Strengths of Transfusion Laboratories and Blood Banks

- Harvesting and handling of apheresis and cellular products
- Quality systems with a focus on “processes”
- Product safety focus including stringent donor testing
- Mulitidisciplinary: technologists, similar staff training; microbiologists
- Back-up power supplies

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Equipment/Reagents

- Reliable Maintenance and Availability
- Qualification/validation and monitoring of equipment/reagents
- -70º C product storage in mechanical freezers vs liquid nitrogen: length of storage and viability
- Back up/ Contingency: all need for JACIE!

Important Considerations

- Qualified staff and Training programmes
- How many lab staff are needed: minimum of 2
- to limit each workstation and each staff member to the processing of one product at a time
- Quality systems
- Quarantine

Clinical Focus

- Representation at Clinical Transplant Meetings
- Correlation with engraftment data and clinical outcomes (CD34; TNC; viability; microbiology)
- assurance that the clinical outcomes match the reliability of processing
- Apheresis /processing/ staff /equipment all contribute
- /Threshold of $2x10^6$ CD34/kg and a desirable $5x10^6$ CD34/kg

Required Equipment:

Dedicated:

Biosafety Cabinet	Refrigerator	Balance (Scale)
Water bath	Centrifuge	Freezer (≤ -70^{o}C)
Hematology Analyzer	Tubing sealer	Personal computer
Plasma Extractor	SCD	
Pipette Aid	Hemostats	Tubing stripper
Cryo-transporter	Micropipettes	Label printer

Shared:

Hematology Analyzer	Flow Cytometer	Micro Lab
Microscope	LN_2 Freezer	Reference Thermometer

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Auto vs Allo

- Autologous: freezing capacity and secure storage for the stem cell graft. Largely PBSC based with higher mobilisation failure
- Allogeneic: red blood cell (RBC) and plasma depletion services and be prepared to thaw and infuse cord blood products. DLIs

- Is Autologous processing more challenging?
- Allo products if given fresh actually needs less doing than auto except for plasma/red cell depletion in ABO mismatched transplants. If PBSC-only plasma depletion and this often not mandatory

What else to be considered

- Post thaw viability
- Sterility testing
- Non conforming product
- Bedside vs lab thawing
- Adverse effects
- Registry of all facilitites processing stem cells
- Cell Therapy for regenerative medicine and its knock on effects

Key partners in Cell Processing / Therapy Organisations

- AABB
- ISCT
- ISBT
- WBMT: FAQs and email
- CTCLAG
- AHCTA
- FACT/JACIE

Discussion

- Transplant programmes and graft processing labs: relationship
- Qualified manpower and training: twinning?
- How should one start? Auto vs Allo. The cell processing perspective
- Costs for running a cell processing lab
- Access to equipment/maintenance, reliability of power and qualified staff. Freezing capacity
- Advanced cell processing

World Health Organization

AIDE-MEMOIRE

for National Health Authorities*

Tissue and cell transplantation represent essential and rapidly developing therapies in modern healthcare. It is the responsibility of national health authorities to ensure that the needs of patients are met with a supply of safe tissues and cells of appropriate and consistent quality. A nationally supported legislative framework which defines consent requirements and supports donation and a regulatory system which authorises tissue and cell banks are prerequisites to achieving this goal. Donation and transplantation activities should be organised in a transparent way with the provision of adequate information and data to enable the public to make informed choices.

Tissue and cell transplantation carry risks of disease transmission. Viruses (including HIV, hepatitis B and C), bacteria, fungi, parasites

Access to Safe and Effective Cells and Tissues for Transplantation

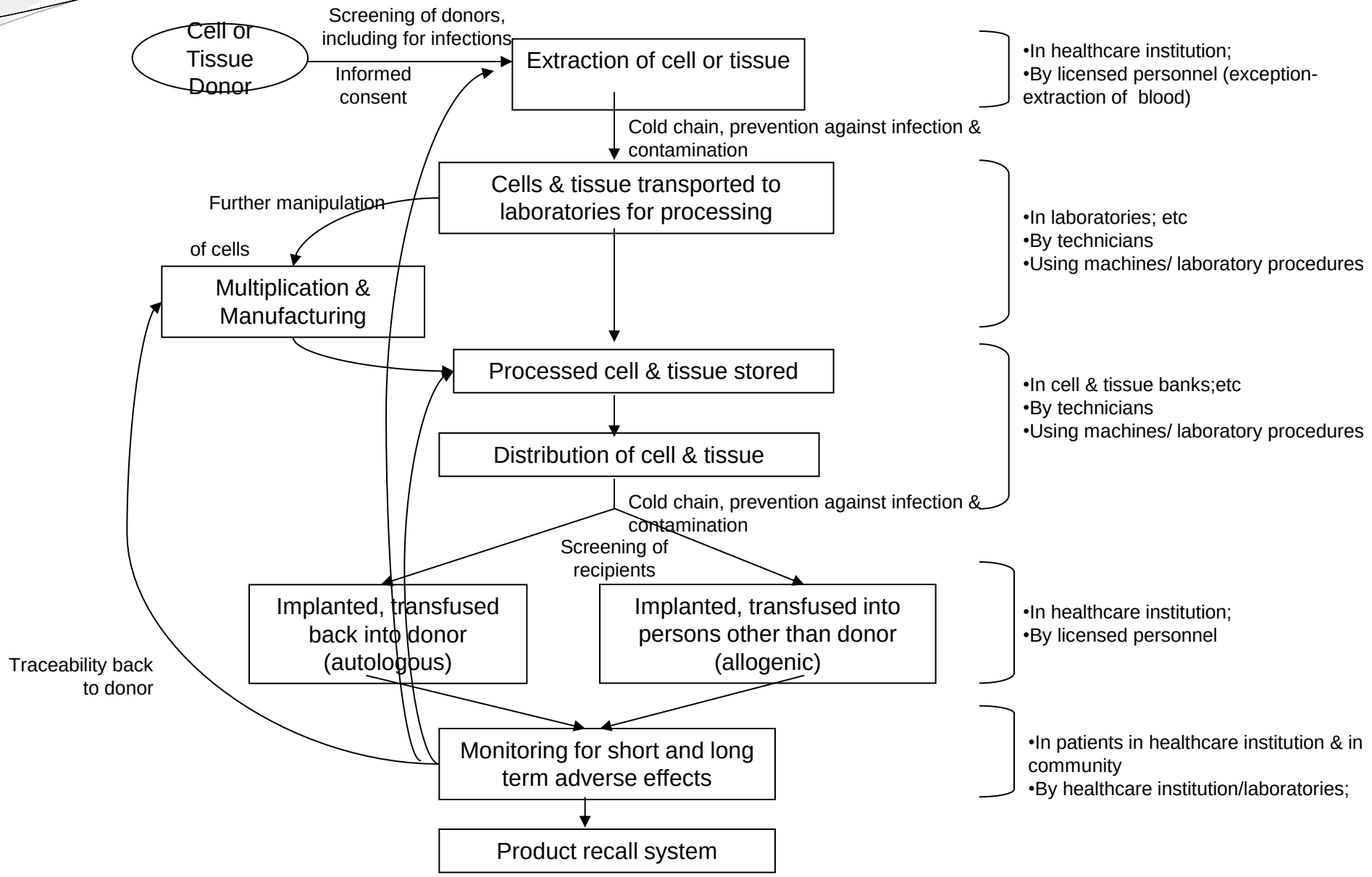
☑ Checklist

National Oversight

- ❑ Legislative/Regulatory framework
- ❑ Appropriate national/international standards
- ❑ Inspection and authorisation of screening, testing, retrieval, processing, storage, distribution, import and export
- ❑ Surveillance and vigilance including transplantation transmitted disease
- ❑ Monitoring and reporting of donation, processing, distribution , import, export and transplantation activity data

Annex A

General flowchart of cell & tissues used for therapy from source to final usage

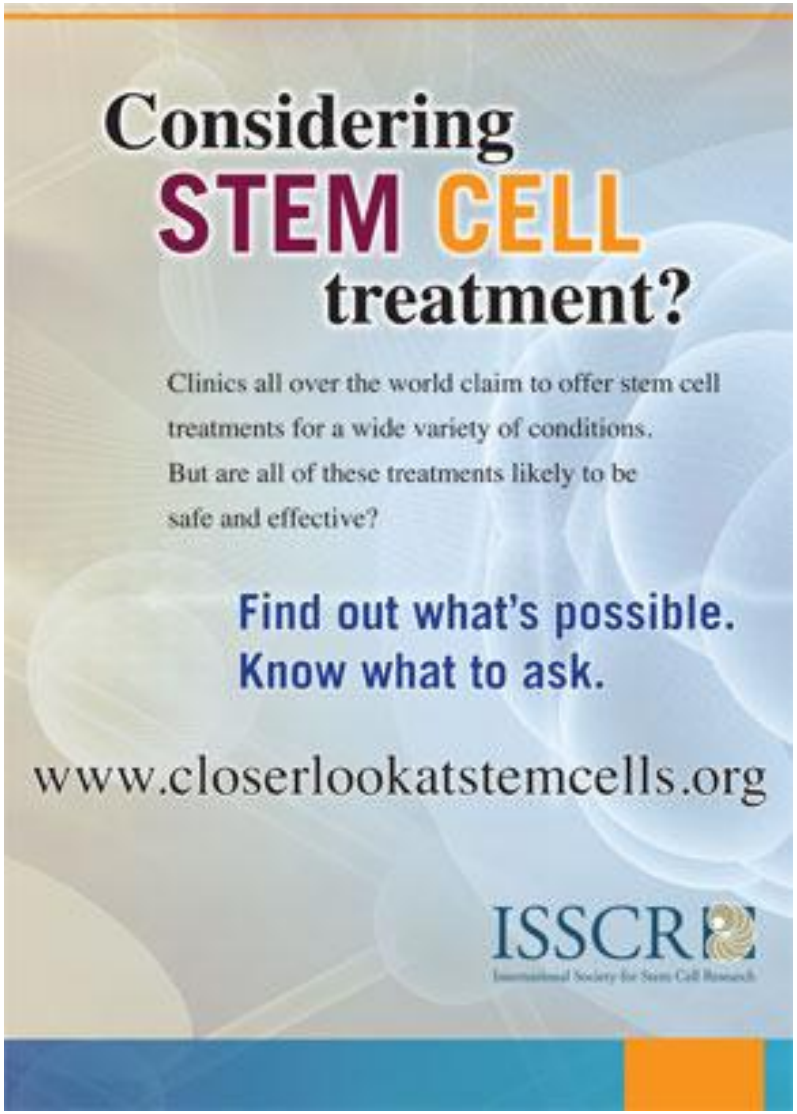


Transport. Import/Export and Regulatory Issues

- Labelling and Cold Chain Transport

- **Country Regulations.**
- Traceability of Stem Cell donations
- Infectious Disease Testing
- Required environment for cell processing

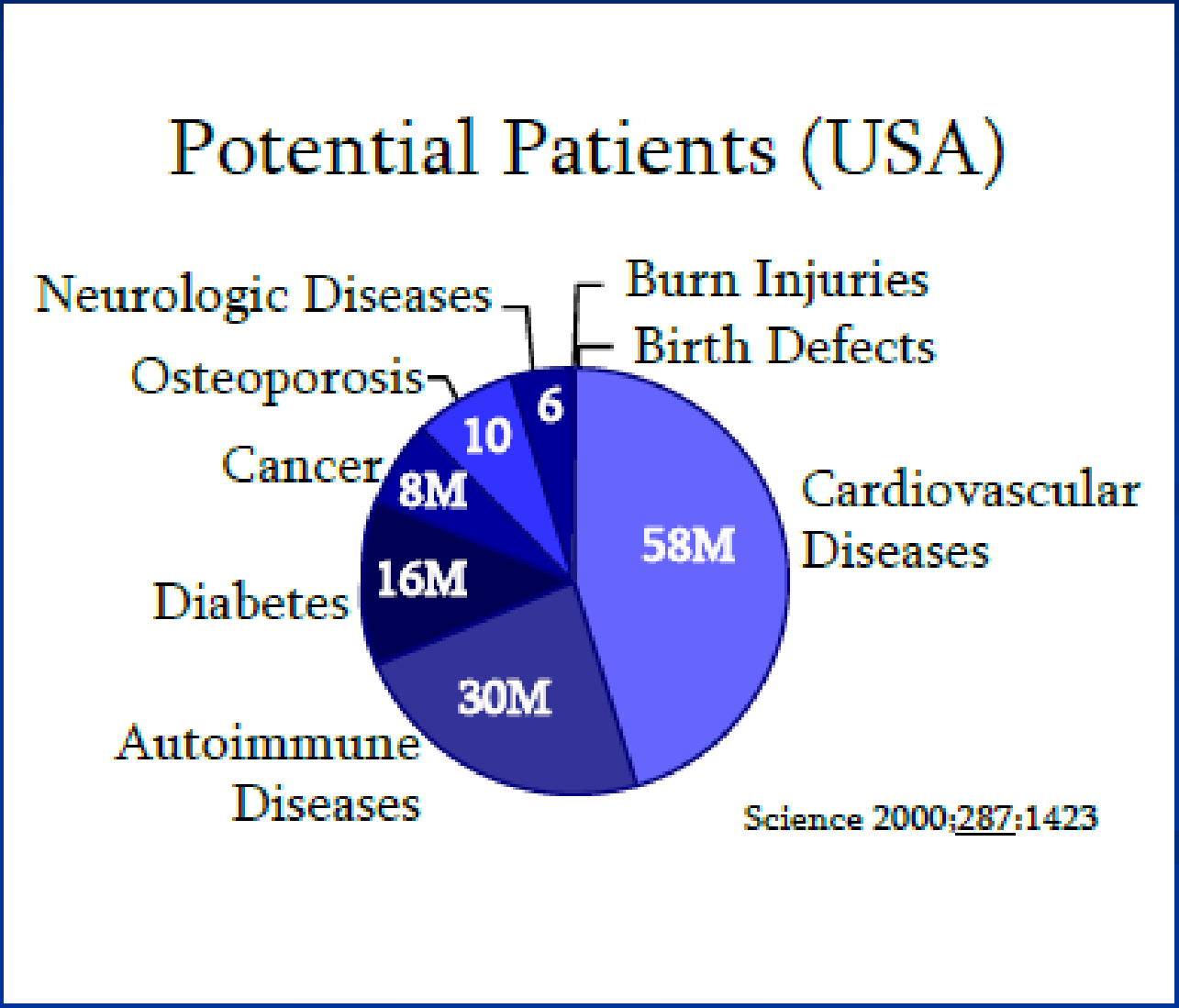
Dealing with cell therapy tourism

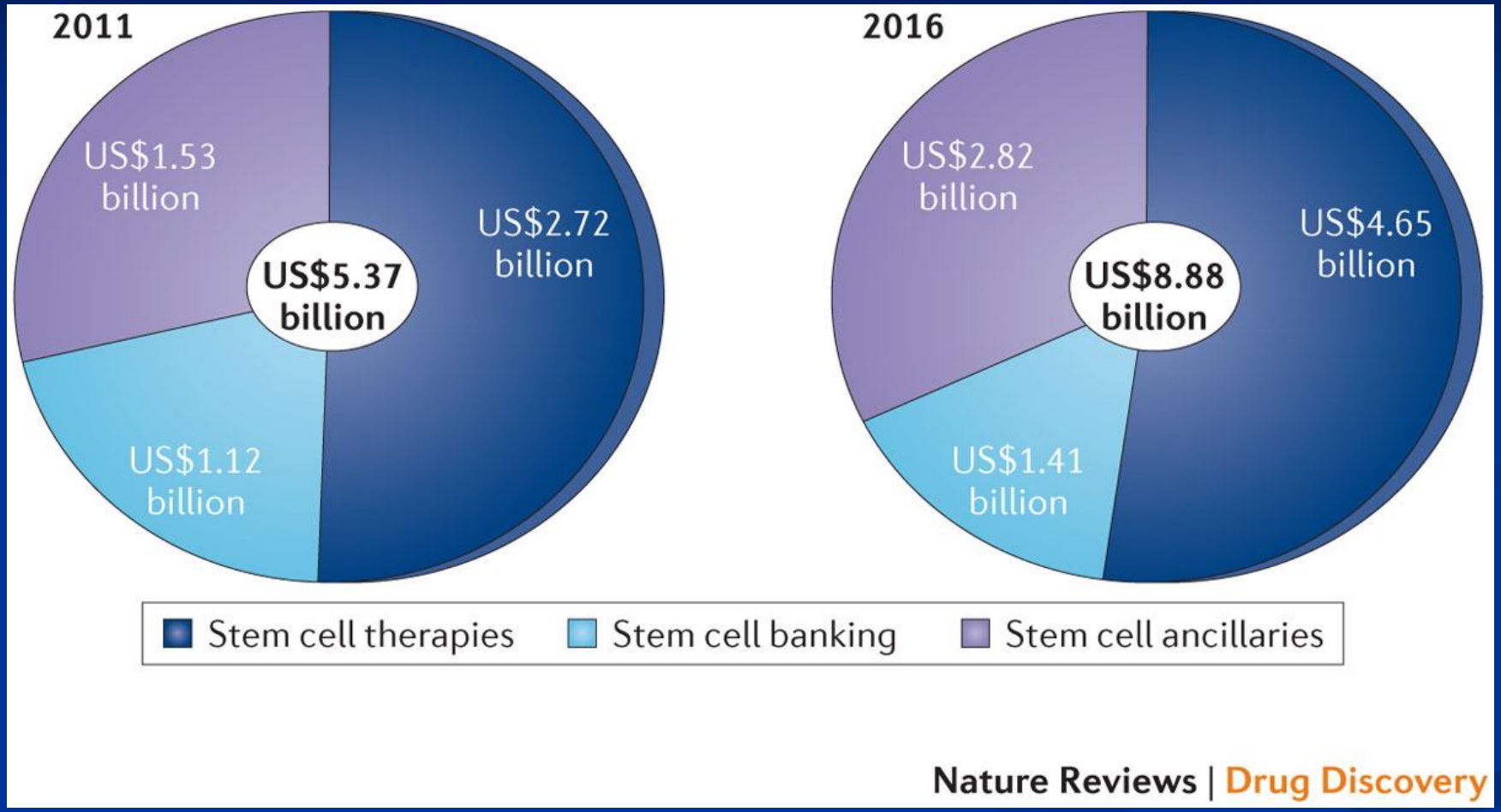


United States

- Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulated by US Food & Drug Administration
- HCT/Ps that meet ALL of the following criteria = “361” products
  - Minimally manipulated
  - Intended for homologous use
  - Not combined with drug or device
  - No systemic effect or not dependent on metabolic activity for primary function
  - ❖ No pre-market approval
  - ❖ Comply with Tissue Rules, including tissue establishment registration
- Other HCT/Ps = “351” products
  - Comply with Tissue Rules
  - Regulated as biologics or device (IND/BLA, IDE/PMA/510K)

Cell Therapy: Potential




2011
US$1.53 billion
US$2.72 billion
US$5.37 billion
US$1.12 billion
2016
US$2.82 billion
US$4.65 billion
US$8.88 billion
US$1.41 billion
Stem cell therapies
Stem cell banking
Stem cell ancillaries
Nature Reviews | Drug Discovery

Attribute	Test Method	Specification
Donor Screening	Summary of Records; Donor Eligibility Form	Donor Eligible
Infectious Disease Testing	Certified Laboratory	Negative (exclusive of CMV)
Infusion Volume	Measurement	≤20mL / Kg / Infusion
DMSO Volume	Calculation	≤ 1mL / Kg / Day
Total Nucleated Cell (TNC) Count	Automated Cell Counter	As Measured
RBC content (if ABO incompatible)	Automated Cell Counter	≤20mL-30mL /Adult Infusion
CD34+ Cell Count	Flow Cytometry	≥ 2 x 10^6 / kg
CD3+ Cell Count (if allogeneic)	Flow Cytometry	As measured
Viability (pre-freeze)	Flow Cytometry	≥ 80%
Sterility	Bacterial Culture	No Growth
Sterility	Fungal Culture	No Growth
Final Product Labeling	Observation	Labeled Correctly